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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/086,542	02/28/2002	Geoffrey M. Wahl	SALK1790-6 (088802-3457)	2411

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EXAMINER	
BERTOGLIO, VALARIE E	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 02/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/086,542	WAHL ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

In view of the Appeal Brief filed on 12/16/2003, PROSECUTION IS HEREBY REOPENED. New grounds of rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) request reinstatement of the appeal.

If reinstatement of the appeal is requested, such request must be accompanied by a supplemental appeal brief, but no new amendments, affidavits (37 CFR 1.130, 1.131 or 1.132) or other evidence are permitted. See 37 CFR 1.193(b)(2).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-19 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-13 of U.S. Patent No. 5,677,177. Although the conflicting claims are not identical, they are not patentably distinct from each other because both

sets of claims encompass a genus of transgenic non-human mammals comprising at least one FLP recombinase target site. The claims of '177, although not specifically drawn to transgenic non-human mammals, encompass mammalian cells in vivo, and therefore encompass the transgenic non-human mammals of the instant invention. Therefore the claims of '177 anticipate the instant claims.

The composition of claims 1-13 of '177 encompasses a transgenic mammal containing at least one FLP recombination target site (pending claims 1,2, and 5-19) and further comprising FLP recombinase (pending claims 3 and 4). Claims 2-5 of '177 encompass a transgenic non-human mammal comprising a FLP recombination target site in a gene of interest and a second DNA fragment comprising at least a second portion of said gene of interest or a portion of a second gene of interest wherein said second DNA contains at least one FLP recombination target site wherein when said second DNA is combined in frame with said first DNA, a functional gene is provided (pending claims 12 and 18). Claim 6 of '177 encompasses a transgenic non-human mammal comprising a FLP recombination target site in a gene of interest and a second DNA fragment comprising at least a second portion of said gene of interest or a portion of a second gene of interest wherein said second DNA contains at least one FLP recombination target site wherein when said second DNA is combined in frame with said first DNA, disruption of said first gene of interest occurs (pending claims 13 and 19). Claim 11 of '177 recites the limitations of pending claim 10 including a transgenic non-human mammal comprising a FLP recombination target site positioned within a gene of interest. Claim 11 of '177 does not teach that the gene of interest is selected from the group consisting of β-galactosidase, thymidine kinase, tyrosinase, and antibiotic resistance. However, the specification of '177 taught the use of

the gene encoding β-galactosidase as a gene of interest in the claimed composition (column 13, line 1; Figure 3A, middle).

Claim Rejections - 35 USC § 112-1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The previous rejection is maintained for reasons of record set forth on pages 2-6 of the previous Office Action, Paper No. 10, mailed 06/17/2003.

Applicant's arguments filed 12/16/2003 have been fully considered but they are not persuasive. In a general respect to the enablement rejection, Appellant argues that "The goal of using the invention FLP recombinase-mediated recombination to produce a transgenic animal was to avoid the very limitations known in the art, for example, random integration of a gene of interest into the genome (refer to Appeal Brief, page 8, paragraph 3, lines 12-15). Appellant emphasizes that the methods of the present invention use FLP recombinase-mediated recombination to introduce a transgene of interest after a FLP recombination target site is established in the genome (refer to Appeal Brief, page 8, lines 5-7).

In response, claims are not drawn to methods, but to products. Specifically, claims are drawn to a product necessary for the use expressed by Appellant- to avoid the limitations inherent in random integration of a gene of interest into the genome. As stated by Appellant, the present invention uses FLP recombinase mediated recombination to introduce a transgene of interest after a FLP recombination target site is established in the genome. However, the specification fails to teach what that genomic location may be or what characteristics it may have. If the initial FLP recombinase target site is randomly integrated, then insertion of a transgene into that randomly located FLP recombination target site, although not random itself, amounts indirectly to random transgene insertion and offers no benefit over direct, random transgene insertion. The specification fails to provide the guidance necessary to insert the initial FLP recombination target site into the genome so as to overcome the unpredictability of random transgene integration.

With specific respect to the insertion of an initial FLP recombination target site to make the claimed mammals, Appellant argues that an FLP recombination target site is defined by its nucleotide sequence and one of skill in the art can readily introduce this FLP recombination target site into the genome using standard techniques (see Appeal Brief, page 9, last paragraph). Appellant argues that one of skill in the art can then determine the site of integration of the FLP recombination target site using standard techniques (page 10, first paragraph). Appellant also argues that incorporation of an FLP recombination target site into the genome does not require any expression and is not subject to position effects (Appeal Brief page 10, lines 22-24).

In response, use of the invention, requires that the FLP recombination target site be inserted into a known, active region of the genome, not just that the identity of a random site be determined. The specification does not provide the guidance necessary to determine how to insert the FLP recombination target site into an active region of the genome or what genomic regions are accessible to FLP recombinase that are transcriptionally active. The specification has not taught any specific genomic site for integrating a FLP recombination target site. As set forth above, the experimentation required to determine if a site of integration is preferable or useful, is undue. Merely having all of the techniques needed to practice the full scope of the claims available in the art is not enabling. The Federal Circuit has cautioned against over-reliance on the rule that a patent need not teach what is well known in the art (See Genetech Inc. v. Novo Nordisk A/S, 108 F.3d 1361,1366,42 USPQ2d 1001, 1005 (fed. Cir. 1997): "[T]hat general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement....It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement."

It is also maintained that the position effect does have a role in subsequent expression of the insertion of a transgene at the FLP recombination target site and therefore, the use of the claimed invention. Applicant states further "the benefit of positioning a FLP recombination target site prior to recombination is that it allows for precise positioning and timing of a recombination event specifically mediated by FLP recombinase, which provides significant advantage over standard transgenic techniques" (Appeal Brief, page 10, lines 24-27).

Again, it is maintained, that the FLP recombination target is not positioned, but is randomly inserted, and for that reason, does not provide significant advantage over standard transgenic techniques (see paragraph bridging pages 7-8 of the office action, mailed 11/06/2002).

With specific respect to the rejection on the grounds that the specification fails to provide the guidance necessary to deliver FLP recombinase to cells of a non-human mammal in vivo to cause phenotypically detectable levels of recombination, Appellant argues that only routine experimentation would be required to optimize the level of FLP recombinase (Appeal Brief, paragraph bridging pages 10-11).

In response, optimization is not all that is required. As set forth on pages 3-4 of the previous office action, the specification fails to provide the guidance necessary to introduce FLP recombinase to cells of a non-human mammal in vivo. The specification merely provides prophetic teachings contemplating that injection, microinjection, electroporation, etc. can be used (see specification, page 12, paragraph 0038). The specification does not teach what to inject or electroporate. The specification does not teach how much to inject or electroporate. The specification does not teach how to deliver FLP recombinase enzyme to the nucleus of cells.

Appellant argues that only routine experimentation would be required to optimize the level of FLP recombinase that would affect recombination at the previously identified position of the genomic FLP recombination target site (Appeal Brief, page 11, lines 1-4).

In response, the Examiner maintains that the specification does not provide the guidance necessary to determine any "previously identified position of the genomic FLP recombination

target site" as argued by Applicant. For one of skill in the art to practice the claimed invention, they would not merely have to screen for transgenic mammals expressing "suitable levels" of recombinase "simply detected by the occurrence of an FLP recombinase-mediated recombination event" (Appeal Brief, page 11, lines 3-4). Detectable levels of recombination are not necessarily indicative of desirable levels of gene expression or that the detectable level of recombination correlates with effective levels, i.e. expression or disruption of a gene to levels that cause a desired phenotype. Applicant sites Dymecki, (1996, PNAS, Vol. 93, pages 6191-6196) as teaching crossing a FLP recombination target site mouse to a transgenic mouse comprising a FLP recombinase transgene and causing recombination at the FLP recombination target site (see Appeal Brief, page 11, lines 10-13). As an aside, this art is post-filing art and, importantly, the specification does not contemplate introducing FLP-recombinase by mating to FLP-recombinase transgenic mammals. Dymecki taught that although all three lines of mice that were generated showed recombination at the FLP recombination target site in at least some cells of the mouse, none showed detectable transgene activity (beta-galactosidase activity; page 6196, col. 1, lines 40-43). Dymecki determined that recombination had occurred in a population of cells by using PCR (page 6193, column 2, paragraph 3). Dymecki did not teach that recombination occurred even in a majority of the desired cells and was not able to detect expression of the resulting recombined gene. Based on the lack of beta-galactosidase activity detected and the low level of recombination necessary to be detected by PCR, it cannot be determined based on the study of Dymecki, that a reasonable number of cells underwent FLP-mediated recombination. The lack of β-galactosidase activity in the mice could be a result of an undetectable number of cells possessing a recombined transgene.

With respect to the rejection on the grounds that the specification fails to enable integrating a FLP recombination target site into the genome of various species of mammals, Appellant argues that such a task is standard in the art (page 11, last paragraph). Appellant argues that methods of making and manipulating various mammalian ES cells were known in the art at the time of filing.

In response, techniques for making non-mouse species of transgenic non-human mammals are standard in the art but results in random transgene insertion, which fails to provide the asserted utility of the invention. Furthermore, the specification fails to provide working examples correlating to a single mouse, rat, monkey or hamster as claimed (see claims 15-19). In order to use the claimed in vivo invention, germline transmission of transgenes is necessary. First generation non-human mammals are chimeric and without germline transmission, non-chimeric transgenics cannot be made. Appellant points out that one of the Examiner's own references (Mullins, 1996, J. Clin. Invest., Vol. 98, pages S37-S40) illustrates pluripotent rat, sheep and cattle ES cells capable of producing chimeric offspring and that this is all that is required by the claims (Appeal Brief, page 12, lines 1-3). The Examiner argues, however, that use of the claimed non-human mammals requires non-chimeric mammals. The specification does not enable one of skill in the art to use a chimeric mammal comprising a FLP recombination target site as the phenotype of said chimeric is unpredictable for reasons set forth above and in the previous office action (pages 4-5). One exemplification of the necessity of totipotent ES cells in the instant invention is in generating a non-human mammal with a targeted FLP recombination target site. If pluripotent cells were used to generate a chimeric non-human mammal, it would not be known

mammal, it would not be known which cells of a chimera comprise the FLP recombination target site. If one were to use random insertion of a FLP recombinase target site to generate chimeric mammals, that target site, once determined to be appropriately located, could not be propagated to successive generations for FLP-mediated recombination at that site. To date, the only cells known to contribute to the germline of an animal are mouse embryonic stem cells (refer to Mullins, 1996) and therefore, the specification fails to provide the guidance necessary to generate the claimed species of non-human mammal other than mouse.

Appellant further argues that the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim (Appeal Brief, page 14, last paragraph, lines 1-2).

It is maintained, however, that the specification is drawn to in vitro methods that fail to correlate with the claimed in vivo subject matter. Transfection of cells with DNA in vitro is an entirely different technology than transfection of cells in vivo and requires vastly different technical considerations. One can readily transform a vast majority of cells in culture with plasmid DNA. Expression of a transgene encoded on the multiple copies of the plasmid that enters each cell occurs transiently at levels that differ from that of stably incorporated transgenes in vivo. Furthermore, one can control the temporal expression of FLP recombinase in vitro by transforming cells at a desired time point. The only means of temporal control in an in vivo situation is by use of specific promoters, which the specification fails to describe, and the activity of which is unpredictable (see pages 4-6, specifically page 5, lines 8-17 of the office action mailed 11/06/2002). Finally, in an in vitro situation, one can control the timing of a

recombinational event with an exogenously added DNA merely by controlling the time of cell transfection. In vivo, if it is desired to insert a DNA into the genome at a desired time point in the life of an animal, one would need to know how to deliver the DNA to the desired cells at the desired time point, in vivo. Thus, the specification lacks any guidance that is necessary to correlate the in vitro examples provided with the claimed invention in vivo, hence the grounds of rejection based on the unpredictability of expression of randomly integrated transgenes in transgenic mammals and the grounds based on in vivo gene delivery (see above).

It appears Applicant has failed to respond to the rejection on the grounds that the specification fails to provide the guidance necessary to deliver a transgene comprising an FLP recombinase target site to cells of a non-human mammal in vivo (refer to page 5, last paragraph of the previous office action).

For the reasons stated above, Appellant's invention amounts to a wish to know rather than an actual reduction to practice. The specification fails to describe a site within the genome for integration of the FLP recombination target site, which is necessary for one to make and use the invention according to the asserted utility. Without knowing and setting forth such a site, the invention cannot be used for the asserted utility and provides no use over the standard technique of random transgene insertion known in the art. Appellant fails to provide a correlation between the in vitro examples and the claimed in vivo subject matter. Specifically, Appellant fails to teach how to overcome the unpredictability set forth in the art with respect to transgene expression, i.e. FLP recombinase transgene, as well as fails to teach how to deliver DNA to cells

in vivo for insertion into a FLP recombination target site. Thus, for the reasons given above, it would require undue experimentation for one of skill in the art at the time of filing to implement the invention as claimed with a reasonable degree of success. Accordingly, the previous rejection is maintained for the reasons of record.

Claim Rejections - 35 USC § 112-2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 12 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 12 recites the limitation "said second DNA" in line 7. There is insufficient antecedent basis for this limitation in the claim.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Fri 6:00-2:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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PRIMARY EXAMINER

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